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ON THE MODE OF ACTION OF IRON

AND THE

RELATIVE VALUE OF ITS SALTS

IN THE

TREATMENT OF ANÆMIA,

BY

GEORGE HERSCHELL, M.D. Lond.

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ON THE MODE OF ACTION OF IRON AND THE RELATIVE VALUE OF ITS SALTS IN THE TREATMENT OF ANÆMIA.

A Paper read by Dr. George Herschell *at the Meeting of the West Kent Medico-Chirurgical Society, November 2nd, 1894.*

The object of the present paper is to discuss the manner in which iron and its preparations act upon the organism, and to try and reconcile to some extent the many conflicting opinions which exist at the present day. It may be now taken as settled that iron administered by the mouth is *really* absorbed into the system, and that the two other theories as to its action, viz., the stimulation theory and Bunge's theory, are erroneous. This has been proved by the very valuable investigations of Stockman.*

~~This~~ theory supposed that in cases of chlorosis the mucous membrance of the intestine was in such a condition that it was unable to absorb the organically combined iron contained in the food. That the iron taken as medicine acted simply as a tonic upon the mucous membrane, and enabled it to do its work in a more efficient manner.

Stockman has definitely disproved this theory by finding that the subcutaneous injection of iron will cure anæmia and

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* "The Treatment of Chlorosis by Iron and some other Drugs," by Ralph Stockman, M.D., F.R.C.P.E., *Lancet*, April 29th, 1893.

chlorosis. He reports four cases, of which the following is an abstract :—

Case 1.—Improvement in hæmoglobin 28% in 24 days, with 12 grains of iron altogether during the duration of the treatment in divided doses.

Case 2.—Improvement in hæmoglobin 32% in 24 days with 6 grains of iron.

Case 3.—Improvement in hæmoglobin 30% in 26 days with 9·5 grains.

Case 4.—Improvement 26% in 32 days with 11 grains of iron.

To quote his own words :—"The evidence, therefore, is overwhelming that iron will cure some forms of anæmia without ever having had the opportunity of stimulating the alimentary canal."

Bunge's theory was briefly as follows :—He held that iron could not be absorbed from the alimentary canal in an inorganic state. That the quantity of iron in a healthy body was kept up to normal by the absorption of organic iron from the food. That in cases of chlorosis the sulphuretted hydrogen and alkaline sulphides formed in the intestine during the process of digestion combined with the organic iron of the food, converted it into insoluble sulphide, and thus prevented its absorption. He believed that when inorganic iron was given in medicine it used up the free sulphuretted hydrogen and sulphides, and thus allowed the organically combined iron of the food to have an opportunity of being absorbed.

Stockman has proved that this theory is erroneous by the simple method of administering ready-made sulphide of iron to anæmic patients, and providing that it should reach the intestine unchanged by enclosing it in capsules of keratin, a substance which is not acted on by the gastric juice. This sulphide obviously could not take up any more H_2S, and as all the patients rapidly recovered it was evident that Bunge's theory could not stand, and that the iron must really have been absorbed into the system.

What happens to the different preparations of iron when they are taken into the body by the mouth ?

The following extracts from the authoritative textbook of Mitchell Bruce* may be taken to fairly represent the teaching of the schools :—

"In the stomach all the salts of iron whatever their nature are converted into the chloride, and do not combine with the acid albuminates like some of the other metals" (p. 84).

"Iron very slowly enters the circulation along the whole

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* "Materia Medica and Therapeutics, 1889."—Cassell & Company.

alimentary canal, as the chloride and alkaline albuminate" (p. 85).

"Iron is excreted by almost every possible channel. As it is absorbed, so a portion of it is excreted along the whole length of the intestine, and colours the fœces black" (p. 86).

"Let it be observed that the solid preparations of this class form soluble compounds in the stomach for absorption into the blood as readily as do the fluid preparations" (p. 87).

This all looks very nice and simple, but I must venture to say that I do not think with the facts before us we are justified in making such definite statements. The subject on close study is shown to be much more complicated.

For instance, I very much question whether all the salts of iron *are* converted into the chloride in the stomach. I fail to see why the contact of weak hydrochloric acid in the stomach will convert an insoluble sulphide into a chloride when it will not do so in a test tube. Also I do not think that we have any evidence that the sulphate is changed at all in the stomach.

As an example of a preparation of iron, which is certainly not changed into a chloride in the stomach, we have dialised iron. It is a fact not generally known by prescribers that the addition of a weak hydrochloric acid to this immediately throws down the iron in the form of the oxide. Any one can try the experiment for himself. I certainly do not agree with Mitchell Bruce in his statement that the solid preparations in the class containing ferric carbonate form soluble compounds in the stomach as readily as do the fluid preparations. It requires *strong* hydrochloric acid to dissolve such a salt.

I propose to take a few of the principal preparations of iron used in medicine, and discuss the probable changes that they undergo in the alimentary canal.

All preparations of iron may be divided into the following groups :—

1. Those that are unchanged in the stomach.
2. Those that are converted into chloride by the hydrochloric acid of the gastric juice.
3. Those that are decomposed and form precipitates.

Of course, if the stomach happens to be empty we can imagine that any preparation of iron taken into it will remain unchanged, and pass thus into the intestine.

The forms of iron which will undergo no chemical change in the stomach will be :—

(*a*) The chloride. This, of course, is obvious.

(*b*) The sulphate. The hydrochloric acid cannot replace the sulphuric as it is the weaker.

A certain percentage of these salts will be absorbed into the system directly from the stomach. Absorption takes place rapidly from the stomach, so much so that it has been

stated that most of the peptone formed in the stomach is absorbed before the chyme passes into the duodenum. It is quite certain that iodide of potassium is very rapidly absorbed from the stomach, as it appears in the saliva in a very short time after it has been swallowed. The greatest area of absorption is undoubtedly the small intestine in its upper half. I believe that the absorption of chloride of iron from the stomach must be in abeyance during the digestive period. It seems very hard to believe that all the time that the stomach is actively engaged in pouring out a secretion of hydrochloric acid at the same time it can be exercising an elective action and absorbing chlorides back into the vessels. And the difficulty is increased if we accept the modern theories as to the mode of formation of the acid of the gastric juice. The acid is said to be secreted by the parietal cells of the gastric glands, and to be formed by the splitting up of the chlorides that the mucous membrane has taken up. The active agent in this decomposition is supposed to be lactic acid, which splits up the chloride and sets free hydrochloric acid. And, since any chloride of iron that is absorbed directly from the stomach must necessarily pass through this mucous membrane, I do not see how it can escape being also destroyed.

As regards the sulphate of iron the process of absorption would be easier, as it would not be decomposed, and would be taken up and absorbed from the stomach like other solutions of watery salts. But taking everything into consideration I think that we are justified in assuming that in most instances very little, if any, absorption of iron salts will take place in the stomach, and that the great bulk will pass through with the chyme into the small intestine. What will happen to our chloride and sulphate there? They will come into contact with the sodium carbonate of the succus entericus, and at once be precipitated as carbonate of iron. This is then probably converted into the alkaline albuminate and absorbed into the circulation, where it unites quickly with the blood corpuscles.

Group 2. Forms of iron which are converted into chloride by the HCl of the gastric juice.

These will comprise :—

(*a*) All iron salts formed by weaker acids than hydrochloric. The acetate, arseniate, bromide, carbonate, iodide, oxide, phosphate, hypophosphite, and the scale preparations.

(*b*) Metallic forms of iron, such as iron reduced by hydrogen. These will be all converted into iron chloride, which will behave in every way exactly the same as the same salt taken by the mouth in the first instance, except that it will be less corrosive.

Group 3. Preparations of iron which are decomposed in the stomach and form precipitates.

It is hardly realised by practitioners of medicine that certain

preparations of iron, which they are in the habit of administering under the idea that they possess distinct advantages, have absolutely no superiority over the common oxide. The forms of iron to which I refer are the following :—Liquor ferri albuminati, liquor ferri chloroxidi, liquor ferri dialisatus, and liquor ferri peptonati. Almost all of the trade-mark preparations of iron with which the market is just now flooded, and which are so extensively advertised, are of this class. Such are—to take a few preparations at haphazard from the advertising columns of the journals—the Iron Malasci, the Liq. ferri-mangan peptonati Bude, Fer Bravais, Hæmoferrum, and Hæmoglobin.

All these substances are in such a state of unstable equilibrium that the addition of a weak hydrochloric acid results in an immediate precipitate of oxide of iron.

This oxide is not soluble in a 2% solution of hydrochloric acid in a reasonable time ; it must therefore pass unaltered into the small intestine.

The significance of this fact is very great. It means that no absorption of a preparation such as dialised iron can *possibly* take place in the stomach. Indeed, no one in his senses could expect that a colloid iron could do so. It means that dialised iron is one of the worst preparations of the metal that we can give, only equalled by the peptonate, albuminate, *et hoc genus omne.*

Yes, but some of my readers will say, if the iron, no matter how you give it by the mouth, has to be eventually all converted into the albuminate in the intestine, shall we not facilitate matters by giving it already changed into its salt?

I must again repeat that *not a particle of the albuminate given by the mouth ever reaches the duodenum as such.* It is precipitated the moment it reaches the stomach into the insoluble carbonate, and this only becomes albuminate again when it has remained for some time in contact with the sodium carbonate and the albumen of the food.

But the question now arises—If all the different forms of iron are eventually converted into the carbonate before they are absorbed, in what way can one be superior to another?

The answer is that there is more than one kind of carbonate.

The carbonate that is produced by precipitating chloride of iron in a test tube, washing and drying, is a very different thing to the one produced by the action of the succus entericus in the presence of the partially digested food. It is a fact well known to chemists that the freshly made or nascent carbonate of iron is in a ferrous state and as such is more ready to enter into new combinations than when in a ferric. It is impossible to preserve ferrous carbonate for any length of time without its passing into the ferric form. And so the iron car-

bonate that we give by the mouth is invariably in the ferric state and insoluble without a great deal of difficulty in the acid of the gastric juice.

Theoretically the best form of giving iron would be the chloride, as this is the condition into which most of the forms of the metal are changed in the stomach, but practically we find that the solution of the chloride as met with commercially contains an amount of free acid that unfits it for giving the best results internally on account of its astringent action on the stomach. The problem of how to find a chloride without astringency is met by the simple precedure of allowing it to be formed in the stomach itself by the action of the gastric juice on nascent carbonate of iron also formed in the stomach as by the decomposition that takes place when sulphate of iron and carbonate of potash are introduced separately into the stomach.

We do this when we administer Blaud's pills in their modern form.

Having seen how far theory helps us in the selection of the best preparation of iron, we will now ascertain in what degree clinical experience coincides with the results that we have arrived at.

In 1892 and 1893 I conducted an investigation with the object of ascertaining if possible whether one preparation of iron had any advantage over another in the treatment of the anæmia so frequently met with in young women. The results that I have obtained I think are sufficiently constant to warrant us in arriving at a definite conclusion.

By a curious chance Dr. Andrew Smart had also during the same time been trying to work out the same problem at the Royal Infirmary of Edinburgh, and has been fortunate enough to forestall me in the publication of results.*

The conclusions at which he has arrived are mainly in accord with my own, but I must venture to differ from him on the following points :—

(1) I have not found in practice that it is possible to give the very large doses of the sulphate that he advocates, with very few exceptions patients refusing to continue them after a few days on account of the gastric disturbance induced.

(2) Judging from my own experience he has left off treatment *months* before he ought to have done. I have always found that if you leave off the iron as soon as the hæmoglobin becomes normal the patient invariably relapses. The length of time during which the patients were under treatment is misleading and calculated to give rise to expectations which will not be realised in actual practice.

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* "On the treatment of Anæmia and Chlorosis by the chief Iron Preparations commonly in use," by Andrew Smart, M.D., F.R.C.P.—*Lancet*, February 18th—25th, 1893.

Dr. Smart's investigations were conducted on cases of symtomatic anæmia, chlorosis, and pernicious anæmia, and he reports in all 15 cases.

In my own experiments I have limited myself to cases of anæmia in young girls, and have noted the action of iron in a much larger number, viz., 65.

In order to compare the relative effects of the different preparations of iron which were made use of by Dr. Smart, I have taken the liberty of averaging his figures and the results, although of course not absolutely accurate on account of the few cases on which he bases his conclusions, yet will serve well enough to point out the relative rapidity with which the blood was restored to normal in the various cases.

He gives the first place to *sulphate of iron,* given presumably in seven-grain doses three times a day, and says that the patients recovered more quickly under its use than under any of the other preparations of iron. He reports eight cases treated with it. By adding together the number of blood corpuscles of these eight patients at the commencement of treatment, and dividing by eight, we get the average number of red blood corpuscles at the commencement of treatment, which was 2,321,250

Obtained in a similar manner the average at the end of treatment was 5,278,750

giving average of improvement 2,957,500

Again, average amount of hæmoglobin at the commencement of treatment ... ... 28·88%

Average amount of hæmoglobin at the end of treatment... ... ... 70·00%

Average improvement ... . 41·12%

With an average of 30·62 days' treatment.

He ranks next in order the *saccharated carbonate* given in doses of 20—30 grains three times a day.

He reports two cases with an average improvement of 2,150,000 corpuscles and 24·5% of hæmoglobin in 26 days.

He considers the *protochloride* next in value given in three doses of the syrup, each containing 7 grains, three times a day. He reports one case in which there was improvement in corpuscles 2,100,000, hæmoglobin 27%, in 65 days.

Phosphate of Iron comes next in 10-grain doses three times a day. One case is reported in which the improvement in corpuscles was 3,800,000, and hæmoglobin 40% in 49 days.

Peroxide of Iron in 15-grain doses. Improvement in corpuscles 1,920,000, in hæmoglobin 46% in 20·5 days.

Ferri et Quinæ Cit. Improvement in corpuscles 1,520,000, in hæmoglobin 25% in three months.

In order to compare these results, a further calculation is necessary: we must reduce them to a common term. We must find out how much improvement took place in one day

The results come out as follows :—

Average improvement in one day when taking—

		Corpuscles	Hæmoglobin
Sulphate of iron	was	960·58	1·34 %
Saccharated carbonate	,,	877·50	·94 ,,
Protochloride	,,	323·07	·41 ,,
Phosphate	,,	775·50	·81 ,,
Peroxide	,,	936·58	2·30 ,,
Citrate of iron and quinine	was	190.00	·27 ,,

From these calculations we perceive that arguing upon the figures which Dr. Smart has given us he is not quite justified in arranging the relative values of the different preparations in the way he has done. Peroxide of iron should be placed immediately after Sulphate, to which it is actually superior in its power of raising the percentage of hæmoglobin, although as a corpuscle-former it does not appear to be so valuable.

Phosphate of iron also seems decidedly better than the protochloride which he has ranked above it.

He states that his reason for ranking the peroxide so low is that he considers it unreliable. He considers the carbonate almost on a par with the sulphate, but does not say whether he gave the ordinary salt or the nascent carbonate in the form of Bland pill or an analogous preparation. If he gave the former I must say that my experience does not agree with his.

My own investigations were carried out mainly on out-patients attending the National Hospital for Diseases of the Heart, Soho Square.

The method pursued was as follows :—The patients were divided into batches, and each of these was put upon a different preparation of iron. The per cent. of hæmoglobin was taken at the commencement of treatment, and the administration of the drug was continued for 20 days. The average improvement in the hæmoglobin was then divided by the number of days under treatment, and the result I take it may be accepted as giving a fair numerical expression of the power of the preparation under consideration to improve the quality of the blood.

The number of red blood corpuscles was not taken into consideration for the following reasons :—

(1) The cases were all carefully selected and were typical ones of chlorosis.

(2) We therefore should not expect to find a marked diminution in the number of corpuscles, as we all know that the characteristic of chlorosis is the diminution of the hæmoglobin out of all proportion to the number of corpuscles.

(3) It is practically impossible in a large out-patient practice to spare the time for counting the corpuscles, a proceeding which, to be accurately done, requires about twenty minutes, while the estimation of the hæmoglobin only takes about forty seconds.

(4) And lastly, because it was my object to point out to the practitioner the facility of using the hæmometer and the value of the results obtained in informing him of the effect of remedial measures on the system. He is usually deterred from examining the blood of his anæmic cases on account of the amount of practice required to use the corpuscle numerator and the time consumed in doing so.

The instrument that I made use of was Fleischl's hæmometer, made by Reichert. In my own practice this has quite superseded the apparatus of Gowers, to which I find it infinitely superior both in ease and rapidity of manipulation. It may be obtained of Baker, of Holborn, and full directions for its use are sent out with it.

My investigations and the results which I obtained were as follows :—

In every case the Hb (hæmoglobin) in the blood was estimated; the treatment was then continued for 20 days; the Hb was then again estimated.

The sum total of the Hb of all the patients in the batch was subtracted from the sum total at the beginning of treatment. This gave the total improvement in Hb for the whole batch. This, divided by the number of patients in the batch and the number of days during which the treatment was carried out, will give the average improvement in Hb per patient a day.

Ten patients were given 10 grains of ordinary coated Blaud's pill from the hospital dispensary three times a day. The pills had probably been made three months or so previously. The average daily increase of Hb was one-eighth per cent.

Ten patients were given 10 grains of freshly-made Blaud's pill. The daily increase of Hb was nearly one-half per cent.

Ten patients were given three times a day eight grains of compressed tabloids of sulphate of iron and carbonate of potash, which, on wetting, become converted into ferrous carbonate. The increase of Hb was 1·2 per cent. per day.

Separate sets of five patients each were given respectively equivalent doses three times a day of sulphate, chloride and ammonio-citrate of iron. The daily gain of Hb was about one-half per cent. in each case.

Other batches of five each were given the albuminate, dialised iron and Flitwick water. The average improvement per day varied slightly above and below one-eighth per cent.

These results well agree with what we should expect to find. Theoretically the ferrous carbonate should be the best prepara-

tion, and practically we find such to be the case when we can ensure that it reaches the stomach as a *ferrous* salt. With ordinary Blaud's pill, made according to the formula in the B.P., this is not the case, unless taken very shortly after making. The ferrous salt rapidly changes into ferric, and the pill after a few days will be of no more use than the Pil. ferri carb.

Many attempts have been made to remedy this defect, and undoubtedly one of the most successful is that of compressing the dry sulphate of iron and carbonate of potash into tabloids without any excipient. When such a tabloid is swallowed, reaction between the salts takes place on coming into contact with any fluid which may be present in the stomach, and the nascent ferrous carbonate is formed in the viscus itself. Such tabloids are now to be obtained protected by a coating of sugar. If such a tabloid be cut open the cream-coloured contents will be seen instantly to change to the dark-green ferrous carbonate on the addition of a drop of moisture.

As regards the other preparations of iron, those which are changed into the ferric carbonate in the stomach will give no better results than the latter drug. The more soluble salts—the sulphate and chloride—although superior to the ferric, are not so good as the ferrous carbonate. Thus we have the freshly-made Blaud pill mass actually formed in the stomach itself.

The worst way of giving iron is evidently by the albuminate, or peptonate, or dialised iron. We have an explanation of the assertion often made in text-books that these preparations are "well borne" and "do not disorder the stomach," in the fact that they are almost inert since they are converted into insoluble ferr*ic* carbonate in the stomach.

Just at the present moment an attempt is being made to introduce into practice hæmoglobin given internally and other preparations of blood under the mistaken idea that they can be absorbed just as they are from the stomach.

We have only to glance through the advertisement sheets of the weekly medical press to find the advertisements of several such preparations.

These will behave in exactly the same manner as dialised iron or the albuminate. They will be converted into the insoluble ferric oxide the moment they come into contact with the gastric juice.

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